Risks and complications of neuraxial anesthesia and the use of anticoagulation in the surgical patient

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Recognition of the risk of thromboembolic phenomena to patients in the postsurgical period has resulted in the practice of administering prophylactic anticoagulant agents to those patients who are at high risk for this complication. Institution of a perioperative anticoagulant or antithrombotic protocol needs to be considered when a regional anesthetic is proposed as part of, or as the total, anesthetic management of the patient. This article reviews current data on the risks involved in the use of neuraxial regional anesthesia in the care of surgical patients in whom prophylactic thromboembolic anticoagulant therapy is planned. Guidelines are established to help the physician minimize the risks of a neuraxial hematoma forming, monitor the patient for this complication, and optimally treat him or her if a hematoma were to occur.

Regional neuraxial anesthesia is an effective method of producing analgesia, anesthesia, and neuromuscular paralysis to provide excellent intraoperative surgical conditions and, if continued, effective postoperative analgesia. Good perioperative analgesia can reduce the stress response to surgery, protect the myocardium, and limit any adverse neuroendocrine effects. Effective analgesia allows for improved postoperative pulmonary function, decreased time to extubation, and earlier mobilization. Neuraxial regional anesthesia involves the use of either an epidural or intrathecal injection of an anesthetic, an analgesic, or a combination of both. Each technique offers the option of either single dosing or a continuous infusion through a catheter placed at the time of needle insertion.

Contraindications to neuraxial anesthesia include infection at the injection site, bleeding diathesis, known left ventricular outflow obstruction, hypovolemia, and increased intracranial pressure. The procedure involves introducing a needle varying from 16 to 30 gauge with various tips blunted and curved to avoid dural puncture during epidural injection and to avoid cerebrospinal fluid (CSF) leak and subsequent spinal headaches after intrathecal injection. Simple complications include backache attributed to the needle trauma and muscle spasm, and postdural puncture headache as a result of CSF loss leading to intracranial hypotension. More serious complications include systemic hypotension as a result of lost sympathetic tone, and the adverse effects of a spinal block caused by the cephalad spread of the anesthetic. This article focuses on the risks of needle and catheter insertion and withdrawal in patients who have received prophylactic administration of antithrombotic agents.

Spinal hematomas are a rare but potentially devastating complication of neuraxial anesthesia. Bleeding into the spinal canal is especially serious: such bleeding is concealed and, because the spinal canal is a nonexpandable space, the resulting hematoma can develop rapidly to cause spinal cord compression, resulting in paraplegia. The infrequent occurrence of this adverse event has made quantifying its probability difficult. An extensive metaanalysis by Tryba estimated the overall incidence of neuraxial hematoma in all patients undergoing neuraxial anesthesia to be 1:150,000 for epidural injection and 1:220,000 for spinal injection (1). These data reflect analysis of 20 case series and over 1.5 million patients. Unfortunately, there was no attempt to further delineate the added risk of associated bleeding disorders, anticoagulation, traumatic or difficult injection, or timing of the catheter insertion or removal in relation to anticoagulant therapy. To assess the risks of causing a spinal hematoma by the use of central neural blockade in the presence of antithrombotic therapy in the perioperative period, there needs to be an understanding of the pharmacokinetics and pharmacodynamics of the antithrombotic agents that may be used. Each agent has unique properties that affect how the anesthetic may be more safely managed.

INTRAVENOUS AND SUBCUTANEOUS HEPARIN

Standard (unfractionated) intravenous heparin exerts its effect by binding to antithrombin III and consequently blocking the effect of thrombin, factors Xa, IXa, XIa, and XIIa, and also factors V and VIII. This form of heparin has a half-life of 90 to 120 minutes, and its activity may be monitored by measuring the activated partial thromboplastin time (2, 3). Coagulation time is prolonged by over 200% 5 minutes after the intravenous injection of 10,000 U of heparin.

Intravenous heparin

Rao and El-Etr conducted a study of 4001 patients undergoing either continuous epidural or continuous spinal anesthesia with subsequent administration of intravenous heparin therapy (4). Patients with a history of leukemia, hemophilia, blood dyscrasia, or thrombocytopenia were excluded from the study. Be-

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fore administration of neuraxial anesthesia, all patients underwent neurological examination by the anesthesiologist and hematologic and coagulation studies (hemoglobin, hematocrit, platelet count, prothrombin time [PT], and partial thromboplastin time). Any patient experiencing a traumatic spinal or epidural needle insertion (i.e., bloody tap) was withdrawn from the study and had no central neural block administered. Heparin was delivered intravenously approximately 1 hour after initiation of the regional anesthesia. The epidural or spinal catheters were removed 24 hours after insertion and within 1 hour before administration of the next scheduled dose of heparin. Twenty patients experienced some form of transient neurological deficit or lower back pain, none of which were permanent, and there were no incidents of recognized spinal cord compression.

Ruff and Dougherty compared the incidence of spinal hematoma in patients undergoing lumbar puncture with or without concomitant heparin therapy (5). Patients with a history of preexisting coagulopathy were excluded. They reported that 2% of the patients receiving intravenous heparin developed a spinal hematoma after diagnostic lumbar puncture with a 20-gauge needle, whereas none of the patients in the nonheparin group developed a hematoma. Complications in both groups were exacerbated by traumatic needle insertion. Additionally, the anticoagulated patient group experienced a higher incidence of complications if anticoagulation was begun within 1 hour of neuraxial needle insertion, and this was exacerbated if the patients also received aspirin. Tryba found that the incidence of spinal hematoma in patients who did not receive intravenous heparin ranged from 1:220,000 (epidural anesthesia) to 1:320,000 (spinal anesthesia) (1). However, the incidence of hematoma formation was 10 times higher in the presence of a traumatic tap and in patients already receiving heparin or aspirin (1:70,000 to 1:150,000).

An important issue is whether surgery should be canceled in a patient with a bloody tap, because the patient is at much higher risk of spinal hematoma if intraoperative or postoperative anticoagulation is planned. To date, no controlled studies clearly address this problem. However, based on a review of the literature, Liu and Mulroy recommended an assessment of the risks and benefits of performing vs canceling the surgery (6). If the decision is to proceed with the surgery, they recommended intensive neurosensory monitoring of the patient in the postoperative period. The catheter should be removed approximately 4 hours after the last dose of intravenous heparin and at least 1 hour before the next dose of heparin.

Subcutaneous heparin

The mechanism of action of low-dose subcutaneous heparin (5000 U every 12 hours) is similar to that of intravenous heparin, in that it inhibits activated factor X and prevents initiation of the coagulation cascade. The maximum effect occurs in 40 to 50 minutes and lasts 3 to 4 hours. The activated partial thromboplastin time may remain in the normal range and is therefore a poor monitor of subcutaneous heparin activity. Low-dose subcutaneous heparin is commonly used in surgical patients and presents little risk of spinal hematoma. Schwander and Bachmann found that of 5000 cases of spinal or epidural anesthesia performed in patients receiving low-dose subcutaneous heparin, no patients experienced a spinal hematoma (7). There have been a few case reports of epidural hematomas associated with subcutaneous heparin, but these occurred in patients in whom the block was associated with some complication such as bleeding at the time of epidural catheter insertion or documented coagulopathy (8–10).

LOW-MOLECULAR-WEIGHT HEPARIN

Low-molecular-weight heparin consists of a variety of fragments of the larger heparin glycoprotein molecule. This fractionation results in more predictable bioavailability (100%), longer half-life, less effect on platelets, and more specific dose-dependent inhibition of activated factor Xa. It is administered subcutaneously twice daily as a 5000-U dose. It can be used for prophylaxis or therapeutic purposes. Peak activity is seen after 3 to 4 hours, and after 12 hours, activity has declined by 50% (11, 12). An early metaanalysis performed in the early 1990s concluded that there was little risk to administering neuraxial blocks to patients receiving preoperative thromboprophylaxis with low-molecular-weight heparin (13, 14). More recently, however, an excess of 50 cases of associated spinal hematoma have been reported, and of these patients, over half became paraplegic following withdrawal of the epidural catheter (15). This increase in reported occurrences has prompted the estimation of the incidence of neuraxial hematoma from central neural blockade to be between 1:1000 and 1:10,000 in patients undergoing orthopaedic procedures who are administered prophylactic low-molecular-weight heparin (12).

DIRECT THROMBIN INHIBITORS

Recently, more selective agents have become available that are direct thrombin inhibitors. Three such drugs are available for clinical use: hirudin, bivalirudin, and argatroban. These agents are frequently used in patients when heparin is contraindicated. It can be assumed that patients using these agents will be at increased risk of developing neuraxial complications in relation to spinal or epidural anesthesia, but little information is available to date.

WARFARIN

Warfarin affects both the intrinsic and extrinsic pathways of the coagulation cascade. It inhibits synthesis of vitamin K–dependent posttranslational gamma-carboxylation of procoagulant factors II, VII, and IX and proteins C and S. Protein C and factor VII have the shortest half-lives, 6 to 8 hours (16). Although PT may be therapeutic within 24 to 36 hours, adequate anticoagulation is not reached until levels of factors II and X are sufficiently depressed. The half-lives of these factors are longer, requiring 4 to 6 days before adequate suppression is achieved. If initial high loading doses (15–30 mg) of warfarin are given for the first 2 to 3 days, desired anticoagulation levels can be achieved within 48 to 72 hours. Although the anticoagulant effects lasts 4 to 6 days after termination of therapy, they can be immediately reversed by transfusing fresh frozen plasma and administering vitamin K (17).

Horlocker et al performed a retrospective study evaluating the risk of spinal hematoma in patients receiving postoperative epidural analgesia while concurrently receiving low-dose warfarin after knee replacement surgery (17). All 182 patients had epidural catheters and received low-dose warfarin to prolong PT to 15 to 17.3 seconds (normal, 10.9–12.8 seconds). The mean PT was within normal range until the third postoperative day and did not reach 15 seconds until the seventh postoperative day. The mean PT at the time of catheter removal was 13.4 ± 2 seconds, and no signs of spinal hematoma were noted. However, because of the variability in patient response, it was suggested that coagulation status should be closely monitored to avoid excessive prolongation of PT during central neural blockade, and in addition, patients with indwelling epidural or spinal catheters should be evaluated routinely for signs of cord compression. They recommend further that if a spinal hematoma is suspected, a magnetic resonance imaging scan should be performed immediately; if a hematoma is found, emergent decompressive laminectomy should be performed.

Wu and Perkins performed a retrospective study to evaluate the risk of developing spinal hematoma with postoperative epidural catheter removal in patients receiving warfarin for thromboembolism prophylaxis after orthopaedic procedures (18). The catheters remained for 43.6 ± 12.5 hours after surgery. They recommended neurological examinations every 30 minutes for the first 2 hours after surgery, every hour for the next 3 hours, and every 4 hours thereafter.

ORAL ANTIPLATELET AGENTS

Inhibition of platelet adhesion, activation, and aggregation is a key component of several major classes of available antiplatelet drugs. These include aspirin and related cyclooxygenase inhibitors that inhibit only platelet activation mediated by thromboxane A_2, therefore allowing activation to occur by other pathways. The development of the thienopyridine class of drugs has enabled the reduction in adenosine diphosphate–mediated platelet activation. Ticlopidine was the first drug of this class available, but its use was limited by side effects such as neutropenia and thrombocytopenia. Clopidogrel, a drug with a better safety profile, is now common therapy in the management of coronary stent implantation. A third class of antiplatelet drugs consists of the platelet glycoprotein IIb/IIIa complex antagonists such as abciximab. Little literature is available on these newer classes of antiplatelet drugs and their potential for increasing the risks of neuraxial complications, but their powerful effects on platelet action must make their use a contraindication for neuraxial anesthesia.

Aspirin produces irreversible acetylation of cyclooxygenase, a key enzyme in the arachidonic cascade, thereby causing its inactivation. At low daily doses (30–300 mg), aspirin inhibits production of thromboxane A_2, a platelet aggregate stimulator and vasoconstrictor, while at higher daily doses (1.5–2.0 g), it inhibits prostacyclin. Thus, aspirin jeopardizes the first 2 steps of hemostasis, vasoconstriction and platelet plug formation, increasing bleeding tendency and prolonging bleeding time for the entire lifetime of the platelets (7–10 days). Nonsteroidal analgesics also influence aggregation of platelets, but this is limited in time to 1 to 3 days after stopping therapy.

Horlocker et al performed a retrospective study of hospital records of 805 patients given 1013 epidural or spinal anesthetics for orthopaedic procedures (19). They reported that no spinal hematoma or postoperative neurologic deficits developed in 391 patients on antiplatelet therapy, including 113 patients receiving multiple drugs. Aspirin was the most common antiplatelet drug used; other commonly mentioned drugs included naproxen, piroxicam, and ibuprofen. They did mention the increased risk of "minor" hemorrhagic complications such as blood-tinged CSF or aspirated blood associated with antiplatelet medications. Age and epidural anesthesia together were associated with a 4.5% incidence of such "minor" complications, but independently they were insignificant risk factors. The conclusion was drawn that preoperative antiplatelet medication was not a contraindication for regional anesthesia.

Horlocker et al performed a prospective study 4 years later in which 924 patients given spinal or epidural anesthesia were studied to determine the risk of hemorrhagic complications associated with regional anesthesia (20). In the study, 386 of the 924 patients took antiplatelet medications; no spinal hematomas were documented in these 386 patients, nor was the incidence of minor hemorrhagic complications increased. Other risk factors, including female sex, advanced age, history of excessive bruising/bleeding, hip surgery, continuous catheter anesthetic technique, large needle gauge, multiple needle passes, and moderate or difficult needle placement, were identified as significant risk factors.

Although antiplatelet medications by themselves may not increase the risk of complications associated with epidural or spinal anesthesia, there is some evidence that combining antiplatelet drugs with heparin therapy may induce spinal hematoma. Litz et al described a case in which a 63-year-old woman undergoing reimplantation of a right knee prosthesis developed a spinal hematoma (21). The patient had received one subcutaneous injection of low-molecular-weight heparin prophylactically and had a measured activated partial thromboplastin time of 33 seconds, a PT of 84%, and a platelet count of $151 \times 10^3/\mu L$. On the day of surgery, no heparin was given, and the epidural was placed preoperatively. Six hours after surgery, a dose of heparin was given. The patient complained of back pain, which was treated with 400 mg of ibuprofen. The patient continued to complain of back pain, so the epidural catheter was removed; 10 hours after removal, the patient developed voiding difficulties. Magnetic resonance imaging revealed an extensive spinal hematoma. Later it was revealed that the patient had regularly taken 500 mg of ibuprofen 4 times a day, and the last dose was 20 hours before surgery. The German Society of Anesthesiology recommends a free interval of 1 to 2 days after the last administration of a nonsteroidal agent and at least 3 days without aspirin before performing central neuraxial blocks. Litz et al echoed this recommendation.

Urmey and Rowlingson reviewed the literature and concluded that antiplatelet drugs by themselves appear not to represent an added significant risk for development of spinal hematoma in patients having epidural or spinal anesthesia (22). The combination of antiplatelet agents with other anticoagulation drugs may increase the risk of bleeding complications. Careful preoperative assessment of the patient to identify complications that might contribute to bleeding is important.

Table. Guidelines for performing neuraxial anesthesia in the presence of anticoagulation or thromboembolic prophylaxis

General principles: Avoid neuraxial anesthesia in patients with preexisting coagulopathy or severe thrombocytopenia. Carefully monitor for signs and symptoms of a developing spinal hematoma during and after initiation of neuraxial anesthesia. During a continuous long-term infusion, maintain an anesthetic level that will permit a neurological examination. The development of a spinal hematoma must be recognized and treated within 8 hours for the patient to have a reasonable chance of neurological recovery.

1. Standard (unfractionated) heparin
   a. Delay heparin administration for 1 hour after needle placement.
   b. Consider the benefits and risks of continuing surgery and anticoagulation if a bloody tap occurs.
   c. Remove the catheter 1 hour before the next heparin dose and 2 to 4 hours after the last heparin dose.
   d. Carefully monitor patients who take prophylactic subcutaneous low-dose standard heparin. No contraindication to neuraxial anesthesia exists in these patients.
2. Low-molecular-weight heparin
   a. Delay needle placement or catheter withdrawal until at least 12 hours from the last dose of low-dose low-molecular-weight heparin and 24 hours after high-dose low-molecular-weight heparin.
3. Warfarin
   a. Determine prothrombin time and international normalized ratio before initiating neuraxial anesthesia in patients receiving a prophylactic dose of warfarin more than 24 hours before surgery. If these values are elevated, the risk of spinal hematoma increases.
   b. In patients who take chronic warfarin therapy, discontinue use and ensure that the prothrombin time and international normalized ratio return to normal range before initiating neuraxial anesthesia. The risk of neuraxial hematoma following epidural catheter removal increases if the international normalized ratio is >1.5.
4. Antiplatelet drugs
   a. Recognize that the use of nonsteroidal antiinflammatory drugs alone does not increase the risk of spinal hematoma. The combination of nonsteroidal antiinflammatory drugs with other anticoagulants may increase the risk of spinal hematoma.
   b. Stop ticlopidine and clopidogrel, platelet receptor glycoprotein IIb/IIIa antagonists, 14 and 7 days, respectively, before neuraxial anesthesia. Their use can be initiated 12 to 24 hours after placement of an uncomplicated neuraxial block.
5. Fibrinolytic and thrombolytic drugs
   a. Since patients receiving both heparin and fibrinolytic or thrombolytic drugs are at high risk of developing a neuraxial hematoma, stop these agents at least 10 days before placement of neuraxial anesthesia.

THROMBOLYTICS/FIBRINOLYTICS

Several thrombolytic or fibrinolytic agents have been in use in the past few years, of which 3 thrombolytic agents (streptokinase, tissue plasminogen activator, and urokinase) have been studied in a limited fashion in relation to neuraxial anesthesia. These drugs work by activating free plasmin, which results in dissolution of fibrin clots, plasma proteins, and coagulation factors. Streptokinase works by binding with plasminogen to create free plasmin and has a half-life of 80 minutes. Tissue plasminogen activator works similarly, but its action is enhanced by binding to fibrin and its half-life is 3 minutes. Urokinase is similar in action to streptokinase. Because of the relatively new use of thrombolytic therapy, there is little information about its safety in patients receiving epidural or spinal anesthesia. However, Rosenquist and Brown reviewed 3 case reports in 1998 and recommended that epidural or spinal anesthesia should be avoided in these patients, except in "highly unusual circumstances" (23). This stresses the need for frequent neurological evaluations, at least every 4 hours, with knowledge by all medical staff of the patient's need for monitoring and familiarity with the proper examination. This monitoring will need to continue postoperatively for 24 hours following spinal anesthesia or for up to 24 hours following catheter removal if the patient remains anticoagulated.

PATIENT OUTCOME

The chance of neurological recovery from paraplegia following spinal cord compression from the development of hematoma has been correlated to the size of the hematomas, the speed at which they develop, the severity of the resulting neurological deficit, and, most importantly, the duration of symptoms. Significant neurological recovery was reported only in those patients in whom decompression laminectomy took place within 8 hours of the onset of symptoms. The report by Vandermeulen et al also showed that at least 50% of all patients with spinal hematomas will have a poor prognosis, with a 26% mortality rate from this complication (9). This can be corrected to a good recovery of neurological function in 50% of patients and a partial recovery in an additional 25% if decompression surgery occurs within the first 8 hours of symptoms. Furthermore, poor outcomes with frequent deaths were reported for those patients who did not undergo decompression (9, 10).

CONCLUSION

Whether to perform neuraxial anesthesia in the setting of prophylactic anticoagulation is a clinical decision. While available data indicate that the incidence of complications remains low, the sequelae of a spinal hematoma can be disastrous and irreversible if not promptly recognized and treated within 8 hours. However, with a thorough initial assessment, a risk-benefit analysis of the need for central neural blockade, careful monitoring, careful catheter placement and removal at the optimal time, and close monitoring of neurosensory signs, the risk of complications from a spinal hematoma can be reduced.

The *Table* provides guidelines for performing a neuraxial block in patients receiving anticoagulant therapy or thromboembolism prophylaxis.

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